Benign Cellular Changes in Pap Smears

Causes and Significance

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OBJECTIVE: We reviewed consecutive cases classified as benign cellular changes (BCC) over a four-month period.

STUDY DESIGN: Cases classified as BCC were retrieved from the cytology files. A search was carried out to identify the previous Pap smears and concomitant cervical biopsies.

In patients with no significant prior cervical neoplasia, BCC represents a wide spectrum of nonneoplastic and reactive processes....

RESULTS: One thousand one hundred three cases (23% of our gynecologic smears) were classified as BCC. Ninety-two patients (8.3%) underwent concurrent cervical biopsies. Specific infections accounted for 8% of BCC cases; reactive changes accounted for 92%. Of the biopsy specimens, 8.3% had no significant pathologic change. The most common biopsy diagnoses were cervicitis (31.5%), immature squamous metaplasia (16.3%) and reserve cell hyperplasia (10.8%). Miscellaneous benign diagnoses accounted for 21.7%. Cervical intraepithelial neoplasia (CIN) 1/human papillomavirus (HPV) was present in 14% of cases. All patients with biopsy diagnoses of CIN 1 had at least two previous abnormal Pap smears. Previous biopsy reports were available for review in 127 (12%) of the 1,103 patients. Of these 127 cases, 53.5% had a previous diagnosis of CIN/HPV; 9.4% had invasive carcinoma. A benign diagnosis was reported in 36.5%.

CONCLUSION: The majority of BCC cases are due to reactive and inflammatory processes. In patients with a previous history of CIN, BCC may be of some significance. In patients with no significant prior cervical ab-

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normalities, a Pap smear classified as BCC represents a reactive process. (Acta Cytol 2001;45:5–8)

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According to the Bethesda System for classifying cervical/vaginal cytologic findings, the category of benign cellular changes (BCC) incorporates two subheadings, infections and reactive changes.[3] To evaluate the usage of this category in our cytology service, to determine the frequency of occurrence of various diagnostic entities composing the BCC category and to evaluate the rate of dysplasia in follow-up on concurrent biopsies in cases interpreted as BCC, we reviewed 1,103 consecutive cases classified as BCC over a four-month period.

The majority of BCC cases are due to metaplastic and nonspecific inflammatory processes.

Materials and Methods

All cervical vaginal cytology cases categorized as BCC from July 1997 to October 1997 were retrieved from the cytology files. A total of 4,764 cervical vaginal cytology specimens were accessioned over this four-month period, and 1,103 (23%) were categorized as BCC based on Bethesda System criteria. A search was carried out to identify the previous Pap smears as well as previous and concomitant cervical biopsies. Previous biopsies over the prior eight-year period were available for review in 127 cases (12%). Of the 1,103 patients, 92 (8.3%) underwent concomitant biopsies due to prior abnormal Pap smears either at our institution (40 cases, 43%) or other ones (52 cases, 57%). The cytologic and histologic diagnoses of these 92 cases were reviewed in detail.

Results

On Pap smears, specific infections accounted for only 12 (8%) cases of BCC. These included *Candida*, 4 cases; *Trichomonas*, 1 case; Herpes simplex virus, 1 case; and predominance of coccobacilli consistent with change in vaginal flora, 6 cases.

Reactive changes accounted for 132 (92%) of the cases of BCC on Pap smears. More common reactive changes included immature squamous metaplasia, 57 (39%); nonspecific inflammatory changes, 26 (18%); and reactive endocervical cells, 26 (18%). Less common causes included parakeratosis, 16 (11%); hyperkeratosis, 5 (3%); typical repair, 3 (2%); and atrophic changes, 2 (1%) (Table I).

The most common biopsy diagnosis was cervicitis, 29 (31.5%), followed by immature squamous metaplasia, 15 (16.3%), and reserve cell hyperplasia, 10 (10.8%). Miscellaneous causes, including microglandular hyperplasia, Nabothian cysts, ciliated cell metaplasia, endocervical polyps, parakeratosis, hyperkeratosis, cervical endometriosis and surface denudation, accounted for 20 (21.7%) of cases. Five (5.4%) biopsy specimens had no significant pathologic change. Human papillomavirus (HPV)–related changes and cervical intraepithelial neoplasia (CIN) 1 were present in 13 (14%) of cases on biopsy (Figure 1). The concomitant Pap smears on these 13 cases did not contain cells diagnostic of low grade squamous intraepithelial lesion (LSIL) on review, and there were no cells that could be classified as atypical squamous cells of undetermined significance (ASCUS). Only mild reactive changes were noted on review, and therefore these cases were classified as BCC and represented "false negative" cases due to sampling. All the patients with a biopsy diagnosis of CIN 1 had at least two previous Pap smears classified as either ASCUS or LSIL.

Previous biopsy reports over the eight-year period were available for review in 127 cases (12%). Of these 127 cases, 68 (53.5%) had a previous diagnosis of HPV-related changes or cervical dysplasia, and 12 (9.4%) had invasive squamous carcinoma of the cervix. Forty (31%) of the 127 cases had benign diagnoses on biopsy, including cervicitis, immature

Table I *Percentage Distribution of BCC Findings on Pap Smears*

Finding	No.	%
Reactive cellular changes	—	92
Immature squamous metaplasia	57	39
Nonspecific inflammatory changes	26	18
Reactive endocervical cells	26	18
Parakeratosis	16	11
Hyperkeratosis	5	3
Typical repair	3	2
Atrophic vaginitis	2	1
Infections	—	8
Candida	4	2.7
Trichomonas	1	0.7
Herpes	1	0.7
Change in vaginal flora	6	4.1

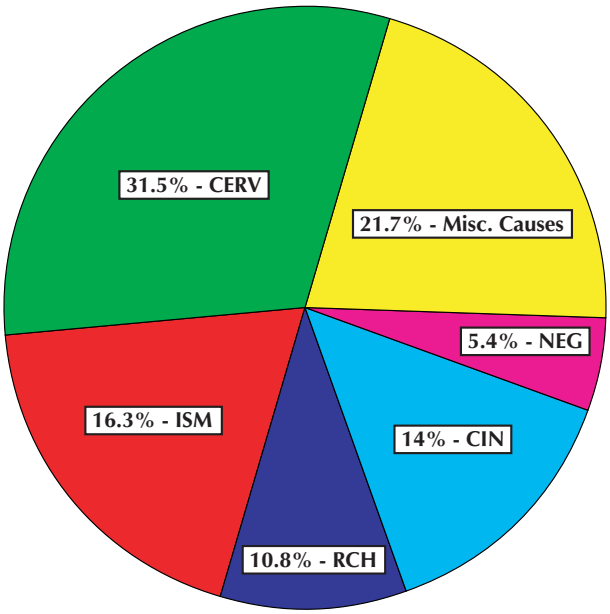

Figure 1 Concomitant biopsy diagnoses in 92 patients with Pap smears classified as BCC. RCH = reserve cell hyperplasia, ISM = immature squamous metaplasia, CERV = cervicitis, MISC = miscellaneous causes, NEG = no significant pathologic change.

squamous metaplasia, reserve cell hyperplasia, endocervical epithelial cell hyperplasia, endocervical polyps, Nabothian cysts, microglandular hyperplasia, etc. Seven (5.5%) of the biopsy specimens had no significant pathologic change.

Discussion

This four-month review revealed that nonspecific reactive and inflammatory changes on Pap smears accounted for the majority of BCC cases. The BCC classification correlated well with the biopsies as the most common biopsy diagnosis was cervicitis, not associated with any specific organisms.

According to a College of American Pathologist survey regarding the proportion of gynecologic smears categorized as "reactive and reparative changes" in different laboratories, 9% of the laboratories had a BCC rate >20% of all gynecologic smears.[6] Twenty-three percent of our Pap smears were classified as BCC during the study period. Our cytology service falls among these 9% of laboratories where the BCC rate is >20%. Of the BCC cases that underwent concomitant biopsies, 31.5% had cervicitis, 16.3% showed immature squamous metaplasia, 10.8% had reserve cell hyperplasia, 14% had HPV/CIN, and 21.7% had miscellaneous benign findings.

Since the introduction of Clinical Laboratory Improvement Act of 1988, policy regarding mandatory review of all reactive cellular changes smears by cytopathologists,[1] the workload of cytopathologists is increased, especially in laboratories where the rate of BCC smears is high. This requirement appears legitimate as most of the small number of BCC cases that were biopsied in this series did show some abnormality, which could be overinterpreted or underinterpreted on Pap smears by the cytotechnologist. Immature squamous metaplasia and reserve cell hyperplasia may produce cells that appear as reactive squamous or endocervical cells and that can be classified as containing benign reactive processes. However, microglandular hyperplasia, ciliated cell metaplasia, reparative processes, endocervical epithelial cell hyperplasia, parakeratosis, treatment effects, foreign body effects and atrophy may pose diagnostic problems and shed cells classified ASCUS. As reported in the College of American Pathologists interlaboratory comparison program in cervicovaginal cytology, the leading cause of overclassification of Pap smears is reactive/reparative changes.[4]

Of the patients who underwent biopsies, 14% had HPV/CIN 1–related changes. All these patients had at least two previous Pap smears classified either as ASCUS or LSIL. The concomitant Pap smears classified as BCC for these patients were reviewed by one of the authors (S.N.M.), and the classification of the findings identified on Pap smears were confirmed. A false negative Pap smear can be due to a variety of factors, including (1) absence of abnormal cells on the specimen slide (sampling error), (2) inability to recognize abnormal cells while screening the slide (microscopy error), and (3) failure in interpreting the abnormal cells accurately by pathologists reviewing the slide (interpretive error). Pap smears from the 13 patients in this category did not have identifiable abnormal cells, and these are considered sampling errors.[2,5]

BCC on Pap smears accounts for a variety of specific and nonspecific changes taking place in the cervix at the time of the Pap smears. These changes may be related to changes in the cervix identified or occurring in preceding years. Specific infections account for a very small percentage of cases classified as BCC. The majority of BCC cases are due to metaplastic and nonspecific inflammatory processes. In

patients with a previous history of dysplasia (CIN), BCC may be of some significance. In this study, 6 (40%) of the 13 cases with CIN/HPV on concomitant biopsies had a prior history of biopsy-proven CIN or cervical carcinoma. The other 54% of patients had ASCUS and LSIL on their Pap smears but no biopsies in our files. Thus, in patients with no significant prior cervical neoplasia, BCC represents a wide spectrum of nonneoplastic and reactive processes taking place in the cervix and is rarely associated with CIN or cervical carcinoma.

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